The Role of Neuregulin 1 in Schizophrenia: A Bioinformatics Approach

Álvaro Machado Dias[1]; Vinícius Maracaja-Coutinho[2]; Artur Trancoso Lopo Queiroz[3]

Abstract. Context: Notwithstanding the great number of studies on the etiology and pathophysiology of schizophrenia, both issues remain far from being fully understood. Schizophrenia seems to be related to several biochemical abnormalities, which point to a multi-factor etiology and pathophysiology, as well as to the perspective that several etiologically diverse disorders might coexist within this nosographic entity. On the other hand, identical twins reveal a high concordance for schizophrenia. From that standpoint, the perspective that structurally-related proteins may play an important and yet non-deterministic role seems attractive. Among these proteins, it is suggestive that Neuregulin 1 exerts a pivotal role. Objective: This paper aims to uncover the most prominent relations that Neuregulin 1 establishes with schizophrenia. Method: Several bioinformatical methods are used in order to present: 1. A visual representation of Neuregulin 1's main molecular pathways, associated with a discussion about their importance to schizophrenia research; 2. A new heatmap of Neuregulin 1 and its receptor's expression in brain tissues most relevant to the understanding of schizophrenia, created after the development of new R programming scripts (described elsewhere), which facilitate the analysis of gene expression profiles in public datasets; 3. A conceptual map of the literature retrieved using the keywords 'Neuregulin 1 and human' in PubMed, followed by a discussion of the most relevant sub-topics. Results: Neuregulin 1 polymorphisms affect several brain tissues and contribute to the etiology and pathophysiology of schizophrenia. Suggestively, Neuregulin 1 partially bridges the 'molecular gap' that schizophrenia establishes in relation to bipolar disorder and Alzheimer disease, which involves genes that affect several brain networks, at the same time that they are highly dependent on noxious environmental variables to be triggered.

Keywords: Schizophrenia; Bioinformatics; Molecular Psychiatry; Genetics.

I INTRODUCTION

Schizophrenia is a severe syndrome that affects around 1% of the world population (Jablensky & Sartorius, 1988). Since the beginning of the 20th century, several attempts to understand its etiology and symptomatological structure have been made, but we still lack a comprehensive picture about these two issues and their mutual relations.

On the other hand, a century of scientific debates certainly produced major advances; currently there is no doubt that schizophrenia is a brain disorder, although there is no such a thing as a 'schizophrenic brain abnormality', as the syndrome was proved to be associated with several types of neuroanatomical abnormalities, each of which contributing in its own fashion to nosology (for a discussion: Dias, et al, 2009). In the same sense, a neurophysiological approach to schizophrenia's etiology leads to a dopaminergic (Fan, et al., 2005), glutamatergic (Gallinat & Gudlowski, 2008; Shim, et al, 2008), Gabaergic (Benes & Berretta, 2001), serotonergic (Abdolmaleky, et al, 2004), and a cholinergic (Raedler, et al, 2006) etiological hypotheses.

On the other hand, it is interesting to note the existence of a 30-35% concordance for schizophrenia among monozygotic twins, which is associated with the well-known fact that schizophrenia frequently runs in families (Kendler & Robinette, 1983). The association of these perspectives suggests that other than neurotransmitter abnormalities may contribute to the etiology and pathophysiology of the syndrome, in a broader and yet not fully understood manner.

Considering all the candidates for that position, the structurally-related protein neuregulin1 seem to be prominent: 1. It is chiefly related with the development of the neurotransmitter systems. 2. NRG1 is one of the most replicated genetic risk factors for schizophrenia –currently there are 202 studies on 'schizophrenia and neuregulin' indexed in Pubmed, which makes it the second most discussed genetic risk factor (after COMT, 285 studies). 3. As we will demonstrate, its expression overlaps some of the most putative brain abnormalities in schizophrenia.

II OBJECTIVES

1. This paper aims to review the most prominent findings related with the expression of NRG1 in the human brain and its main molecular pathways; 2. Analyze the expression of NRG1 in several brain tissues related with schizophrenia's neurological profile; 3. Present a conceptual map of the field of studies on 'neuregulin1 and human'; 4. Systematically review the literature related with neuregulin1 in schizophrenia research.

In a broad sense, the paper aims to apply some of the most advanced bioinformatics methods available in order to collaborate with the efforts to fill the gap that is currently found within the frontiers of molecular biology and psychiatry in relation to neuregulins, neurotrophins, and other non-conventional signaling molecules involved in the neurobiology of psychiatric disorders.

[1] Master, Doctorial Student: Dept. of Neuroscience and Behavior, Institute of Psychology, University of São Paulo. Av. Prof. Mello Moraes, 1721, Zip code 05508-030, Butantan, São Paulo, Brazil. Phone and Fax number: 005511-3091-1901. Corresponding author's email: alvaromd@usp.br.

[2] Doctorial Student: Dept of Biochemistry, University of São Paulo, Brazil. Av. Vital Brazil, 1500, Zip code 05503-900, Butantan, São Paulo, Brazil. Phone and Fax number: 005511-3091-1901. Email: viniciusmaracaja@yahoo.com.

[3] Doctorial Student: Dept of Bioscience, University of São Paulo. Av. Prof. Lineu Prestes, 748, Zip code 05508-900, Butantan, São Paulo, Brazil. Phone and Fax number: 005511-3091-1901. Email: arturlopo@gmail.com.

III METHODS

This paper relies on several data mining and text mining techniques in order to achieve its primary goals, which are complemented by a careful review of the literature. In order to make this paper as comprehensive as possible, each section will present its own context, method, results, and discussion. In that sense, the current section will only provide a preview of these methods.

Section 1 presents a visual representation of neuregulin's main molecular pathways in the Homo sapiens nervous system, which was created using a bioinformatics tool. Section 2 presents an original microarray analysis of the expression of the gene in several brain tissues, based on the development of new parsing scripts. Section 3 uses a data mining/text mining analysis of the whole literature on 'Neuregulin1 and human' indexed in PubMed, in order to provide a conceptual map of the field (3D), which is followed by a review of the sub-topics that relate with schizophrenia, based on the application of a data mining technique in order to define the most influent papers of the current days.

IV RESULTS

1. NRG1 identity and the neuregulin-ErbB pathway

Context: NRG1 is a gene on chromosome 8p12 that produces the neuregulin polyptides, which are part of the Epidermal Growth factors (EGF); it is ≈1.4 megabases long (≈1/2000th of the genome) and encodes proteins in less than 0.4% of itself (Falls, 2003). Neuregulin1 is a member of the tyrosine kinases enzymes, which are proteins that modify other proteins by the addition of phosphates, and that are present in the human genome in 58 different forms (Robinson, et al, 2000).

The word 'neuregulin' was created from the initial names of three different peptides that are controlled by the NRG1 gene: the Neu differentiation factor, the acetylcholine receptor inducing activity, and the glial growth factor (Burden & Yarden, 1997).

The perspective that NRG1 represents a risk factor for schizophrenia became popular after one of the variants of the gene was found in an Iceland cohort of patients (Williams, et al., 2003) known as the carriers of the Iceland haplotype (HAP-ICE).

Later, this finding was replicated in the same population and among Scottish families displaying high rates of schizophrenia (Stefansson, et al., 2003).

Currently, it is believed that NRG1 type I and type IV present the strongest associations with the syndrome (Harrison & Law, 2006), while it is also a fact that the relations that NRG1 defines with schizophrenia and other human disorders are considerably complex and frequently rely on several indirect associations.

Objective: Considering this picture, the current section aims to present a visual representation of the most significant molecular pathways that neuregulin1 comprises in the human central nervous system and to discuss related findings, with a particular focus on schizophrenia.

Method: The visual pathway was created using Genomatix software and curated data. Despite the reliability of the results, we proceeded with a careful analysis of each of the associations, in order to eliminate the less pertinent ones.

Results:

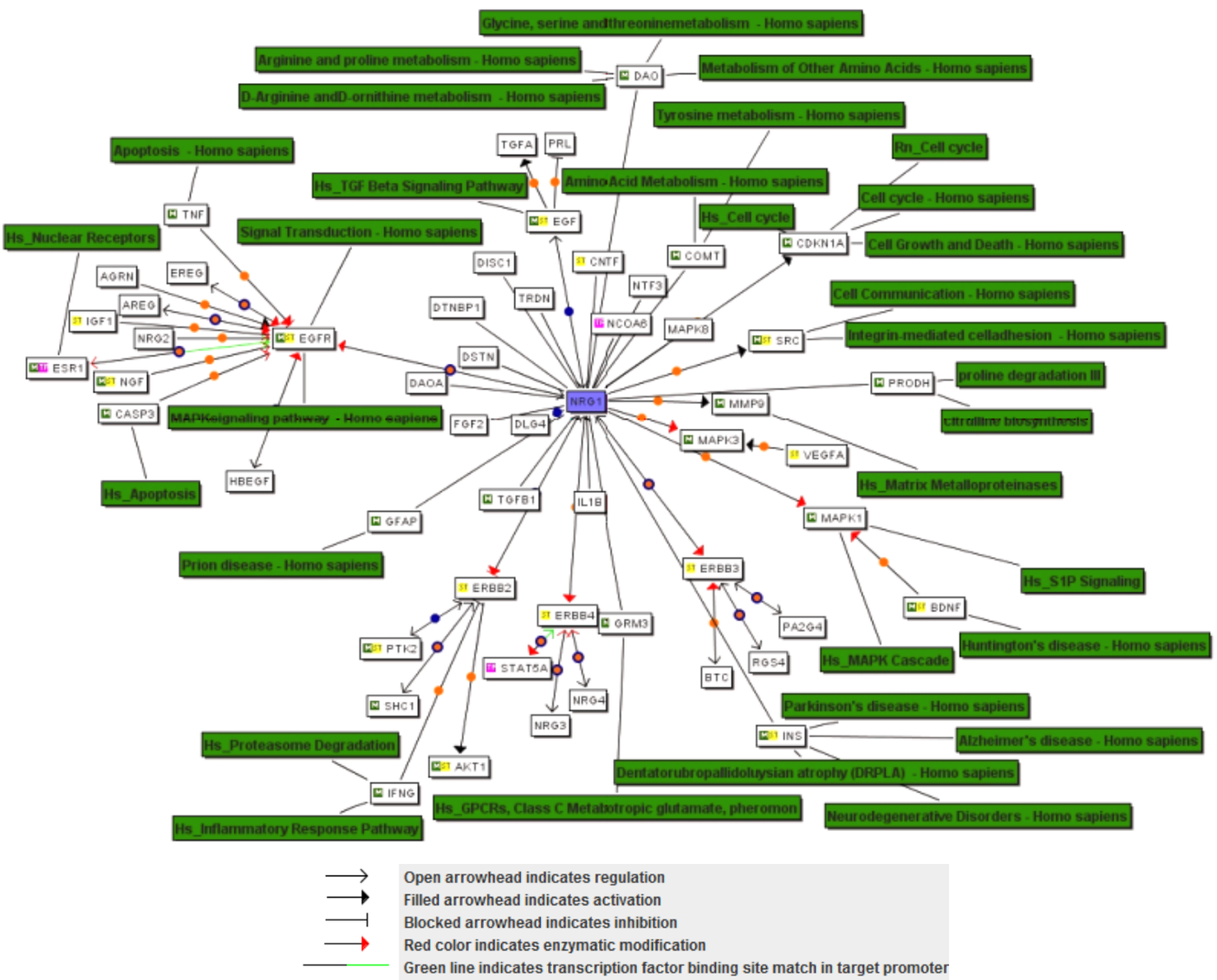

Figure 1: NRG1 molecular pathways.

Discussion: Applying a well known model (Yarden & Sliwkowski, 2001) to the understanding of the above molecular pathways, it is possible to conclude that the neuregulin-ErbB network is composed of three layers:

1. The input layer, mainly associated with the binding effects of neuregulin1 to ErbB3 or ErbB4 (which have an autophosphorylation site), and then to ErbB1 which has no primary biding site.

2. The signal processing layer, wherein each ErbB receptor couples with a specific protein, thus leading to its activation or deactivation, in accordance with associated signaling effects.

3. The output layer, represented by the 'higher order' biological processes (neuronal plasticity; induction of cellular development, programmed death, etc.), which are based on complex cellular interaction and frequently depend on additional interactions (Yarden & Sliwkowski, 2001).

Starting from the input layer, one should note that neuregulin1 phosphorylates various receptors and non-receptors tyrosine knases present on human genome, although only the ErbB type receptor (RTKs) interests for schizophrenia research. In a certain sense, it could be said that the neuregulin1-ErB pathway is one among the ultimate molecular targets of the syndrome: the abnormal increase of free ErbB receptors (a transmembrane protein) is a wide spread finding in the syndrome, associated with several types of signaling dysfunctions.

Within the second layer, it is important to acknowledge that ErbB4 is simultaneously under the influence of NRG1, NRG3 and NRG4, as much as ErbB3 is under multidimensional control, thus suggesting that a narrow approach to NRG1-ErB associations with psychiatric disorders (NRG1 ↓ -ErbB → neurological impair) might not reveal the whole picture that is delineated in the molecular level.

Moreover, as Fox and Korblum suggest (Irina J. Fox, 2005), ErbB1, ErbB2, and ErbB3 are important to GABAergic inhibitory pathways in many parts of the brain through heterodimerization (heterodimer is a two subunits molecule, with one different from the other). A recent study on rodents suggested that the polypeptide is chiefly involved in the formation of the serotonergic pathways (Dean, et al., 2008), while it is a well known fact that neuregulin1 regulates nicotinic receptors synthesis (acetylcholinergic) (Ford, et al., 2003), as much as it is involved in glutamatergic and dopaminergic pathways (T. Karl, 2007).

In terms of the third layer, recent studies suggest that neuregulin1 may inhibit hippocampal LTP (long term memory mechanism) in a temperature-dependent manner (Chen, et al, 2008); deactivate hippocampal LTP by the release of dopamine (D4) in these limbic area (Kwon, et al., 2008); regulate corticostriatal signaling (Chen, et al., 2008); the development of Schwann cells in humans (Cabedo, et al, 2002) and the promotion glial (oligodendrocites) proliferation in the human midbrain (Zhang, et al., 2004).

In neurodevelopmental terms, the neuregulin1-ErbB4 molecular cascade is believed to relate with synapse maturation and neuronal formation, as much as with the maturation of the presynaptic terminals (Krivosheya, et al., 2008). Conversely, decreased expression of neuregulin1 leads to lower dendrite spine density in subcortical areas of the human brain (Chen, et al., 2008).

From that perspective, it is possible to evolve to the 'behavioral level' (disease level), under three different approaches, each of which presenting a particular and significative feature in relation to schizophrenia:

1. In relation to the continuity between normality and schizophrenia, there are finding suggesting that neuregulin1 influences social behavior in a complex and yet unknown fashion (Babovic, et al., 2008; O'Tuathaigh, et al., 2008; Szabolcs Kéri, 2009), which probably involves the ability to cope with environment changes (Steinthorsdottir, et al., 2004). Notably, this ability is notoriously impaired in schizophrenia.

2. In relation to disease-disease interactions, it is significative that Aph1 (anterior pharynx-defective1), which is ultimately related with amyloid beta (and thus to Alzheimer disease -AD) may be related with schizophrenia through neuregulin1 pathways.

An Aph1 type B/C deficiency (Aph1B/C) impairs neuregulin function in several parts of the brain that are chiefly associated with schizophrenia's neurobiological abnormalities, while a Val-to-Met mutation on NRG1 was proved to increase the aforementioned effect, as much as to be reverted by antipsychotic treatment (Dejaegere, et al., 2008). Moreover, another study revealed that both neuregulin1 and ErbB4 are deficient in the hippocampus of these clinical populations (Chaudhury, et al., 2003), suggesting not only that the Aph1-NRG1 is both a schizophrenic and an AD-related pathway, but also that these factors may bridge the molecular gap that separates both disorders.

3. In relation to schizophrenia's endophenotype, a study primarily focused on phosphorylation-dependent and transient PIPs (protein to protein interactions), which was extended to phosphorylation-dependent interactions between neuregulin1 and ErbB4, revealed that neuregulin1 has a significative role in sensorial gating (Wehr, et al, 2008). As one may note, it is possible to associate this last perspective with the fact that schizophrenia is associated with sensorial gating abnormalities, and especially the 'P300 prepulse inhibition deficit' (Wynn, et al., 2004), which impairs the capacity to filter oncoming stimuli during a predefined time windows (300 milliseconds). Notably, Hall and collaborators (2006) found that a missense mutation (single nucleotide) on neuregulin1 rs3924999 is related with prepulse inhibition deficits both in individuals suffering with schizophrenia and non-affected controls.

2. Microarray analysis of Nrg1 –ErbB pathway: a new bioinformatics approach to the molecular cascade under focus

Context: A recent tendency in the genomics approach to psychiatric disorders is the microarray analysis of the genes expressed within the core molecular pathways involved in the disorder's neurobiological profile. This method is strategic as it leads to experimentally supported results believed to be particularly stable in regard to the many datasets previously collected and stored in biological databases.

Objectives: This section aims to present an original analysis of the key genes involved in the NRG 1-ErBb pathway in Homo sapiens neuronal tissues (CNS), in order to contribute with the understanding of its possible role in schizophrenia.

Method: This analysis is supported by a heatmap that was created after the development of ad hoc R programming

scripts, which analyze gene expression profiles in public datasets. Our pipeline parses datasets from the Gene Expression Omnibus database (GEO-NCBI - http://www.ncbi.nlm.nih.gov/geo), in order to select and design a hierarchically clustered set of the genes of interest.
In that sense, we used the following microarray datasets from GEO obtained using an Affymetrix array: GSM182715, GSM182714, GSM182713, GSM182712, GSM182723, GSM182710, GSM182709 and GSM182708.

These datasets comprise respectively the following neuronal tissues from the Homo sapiens CNS: Anterior Cingulated Cortex, Anterior Inferior Parietal Lobule, Anterior Interior Temporal Cortex, Middle Frontal Gyrus, Cerebellum, Caudate Nucleus, Hippocampus and Frontal Pole. Finally, we assumed that, in order to be classified as expressed, a probe needs to have an expression level (P-value) of less than 0.05.
Results: In this analysis we were able to conclude that this pathway represents a fundamental molecular cascade in the biological maintenance and function of the following CNS structures described in table 1 in accordance to the order of importance of the gene expression profile:

1.	Caudate nucleus
2.	Hippocampus
3.	Frontal pole
4.	Cerebellum
5.	Anterior inferior temporal cortex
6.	Anterior inferior parietal lobule
7.	Anterior cingulated cortex
8.	Middle frontal gyrus

Table 1: Neuronal tissues from Homo sapiens CNS in order of importance according their biological gene expression profile.

This hierarchy of expression profiles can be captured at glance through the following figure, generated in our pipeline:

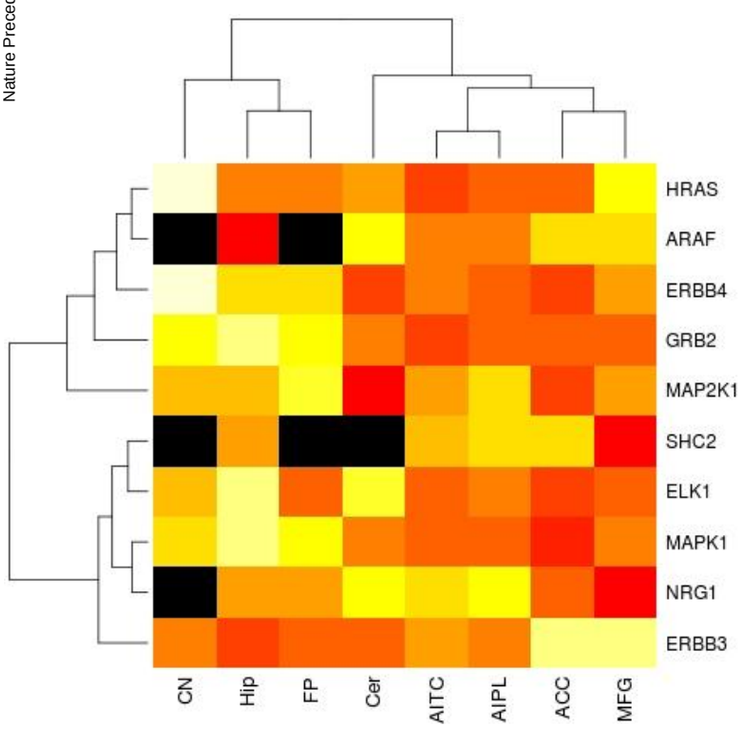

Figure 2: Hierarchical clustering of the key genes involved in the NRG1-ErBb pathway, in Homo sapiens neuronal CNS tissues. The expression levels are represented from light yellow (more expressed) to red (less expressed); while black squares represent the genes.

Discussion: The heatmap indicates the existence of heterogeneity regarding the brain tissues wherein each of the genes involved with the NRG1-ErBb pathway is mostly expressed. In that sense, these expression profiles confirm the perspective that NRG1 may be associated with schizophrenia's neurobiological profile through several indirect associations, which may have been missed by genetic studies focused on an excessively restrictive number of single nucleotides polymorphisms (SNPs).

One interesting finding is that these participants of the NRG 1-ErBb pathway are only modestly expressed in the Anterior Cingulate Cortex (ACC) and the Middle Frontal Gyrus (MFG) of the Homo sapiens. This suggests that up to the extent that the elements of this pathway are involved with the syndrome's neurobiological profile, this has little to do with ACC and MFG abnormalities. Conversely, Caudate Nucleus (CN), Hippocampus and Frontal Pole (FP) are areas of prominent importance.

3. The literature on Neuregulin1 and schizophrenia: systematic review with text mining
Context: Currently there are 603 publications indexed in Pubmed under the keywords "neuregulin1 and human". The huge number of publications in this field of studies makes it unfeasible to rely on personal experience in order to identify and cluster the main concepts under discussion. Moreover, thematic/conceptual clusters based on the absolute number of publications retrieved in Pubmed (e.g. by several searches using keywords that are known to be related with 'hot topics') lead to serious biases.
Objectives: This section aims: 1. To present the results of a semantic text mining analysis, which generated a topological map regarding the representativeness of the main concepts in the field, as much as their associations; 2. To review the main sub-topics that were found in relation to schizophrenia.
Method: This topological map is based on a matrix that implements the degree of relatedness of the concepts that are present in the title, keyword, and abstracts of the indexed papers. To built that matrix, a non linear algorithm was chosen, in order to emphasize the differences between themes (linear algorithms are better on details, but worst on thematic division). Moreover, concepts were fully customized, leading to the exclusion of irrelevant terms, association of synonyms, and hierarchical rearrangement of the main concepts in the field (based on our experience).

A second text mining tool was used in order to calculate a thematic division of the literature specifically related with schizophrenia, which we included in the same figure, inside flouting boxes.

At last, this section presents a review of the themes that were found regarding schizophrenia, which also made use of a data mining technique, in order to select the most prominent papers of the current days.

Results:

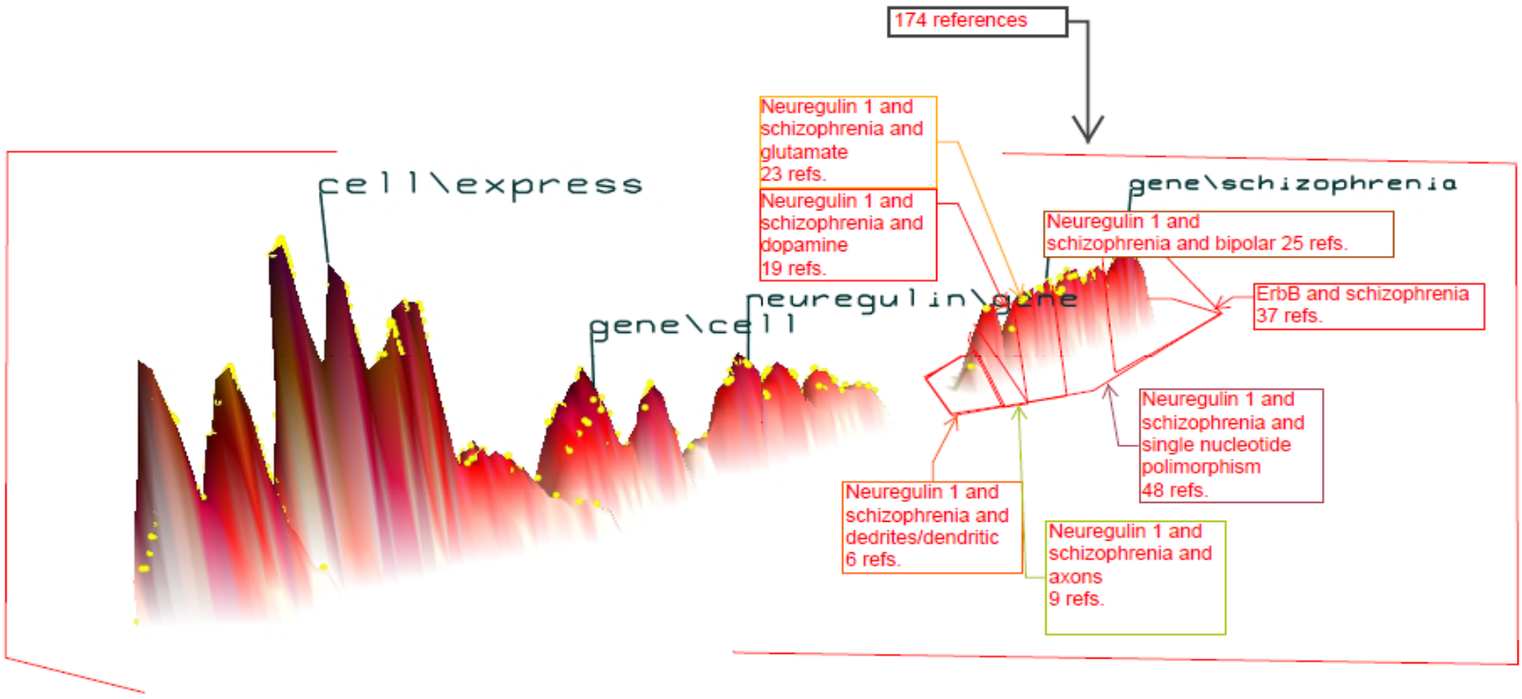

Figure 3: Thematic distribution of the studies indexed in Pubmed under the keywords 'neuregulin1 and human', which was further analyzed for the distribution of 'neuregulin 1 and human and schizophrenia'.

Discussion: The map suggests a division between purely biological studies and the ones related with schizophrenia. Following that suggestion, it is possible to assume the existence of an empty space between both types of studies, which probably relates with the fact that the methodological approaches to both topics are quite different.

Neuregulin1 studies in the context of schizophrenia research (the right group of mounts) relate with disperse tendencies (low peaks, proportionally wide basis), contrary to purely biological studies, which produce proportionally higher peaks. Accordantly, there are 174 studies specifically focused on schizophrenia, which follow the division (relatively disperse) that is presented in the figure and that we will consider in details.

Neuregulin 1, schizophrenia and SNPs

Single nucleotide polymorphism stands for an intra-populational variation on individual nucleotides. Using NCBI single nucleotide analysis tool, 5796 SNPs were found to be linked to human NRG1 (geneID: 3084). After a careful review of the studies on SNPs that are represented in our topological map (48 publications), the main conclusion that can be addressed is that there is a high variability among them. In that sense, the best perspective is to consider the results of a recent and considerably powerful meta-analysis (Gong, et al., 2009), which concluded that only the SNP8NRG221132, 420M9-1395(0) and 478B14-848(0) polymorphisms substantially contribute with schizophrenia's etiology; although this very study also presented a matrix of coancestry which clearly supports heterogeneity.

That said, it might be the case that NRG1 relates to schizophrenia through gene to gene interaction and maybe epistasis, as suggested by the possible association between the Interleukin-1beta gene (IL-1beta) and the SNP8NRG221533 neuregulin1 polymorphism (Hanninen, et al., 2008), whose interaction increases schizophrenia's risk by a 10 times fold rate.

ErbB and schizophrenia

As already mentioned, ErbB4 is one of the core neuregulin1 receptors involved in schizophrenia's etiology. In relation to that, most of the 37 plotted studies that address this section's topic emphasize this perspective.

From that standpoint, a different and highly interesting alternative was presented by a study focused on schizophrenia's viral etiological hypothesis. This hypothesis evolved from findings on the associations between seasonality of birth and schizophrenia (Carrion-Baralt, et al, 2008), which ultimately relate with the fact that influenza, rubella, cytomegalovirus, and other virotic diseases are much more frequent in the fall and winter than in the spring and summer. In that sense, it was suggested that specific genetic risk factors increase the chance of being affected by the mother's viral infection. Considering that, two interesting findings are that ErbB1 (known as epidermal growth factor) is used by the cytomegalovirus (CMV) to gain access to the cells and that the EBP1 factor, which mediates neureguli1-ErbB interaction inhibits influenza transcriptase (Carter, 2008), suggesting a totally new genetic-epigenic pathway for schizophrenia, mediated by neuregulin 1.

Neuregulin 1, schizophrenia and bipolar disorder

It is worth considering that much more is known about the genetic risk factors for schizophrenia than for bipolar disorder (BD). Moreover, the relation between both represents a major conundrum in psychopathology's history (e.g. Kraepelin and Bleuler categorically separated them; Jaspers and Freud were not so straight forward). In that sense, the question of whether the disorders share genetic risk factors represents a matter of special interest. Accordantly, after testing four single nucleotides, Georgieva and collaborators (Georgieva, et al., 2008), found a nominal allele-wise significance for SNP8NRG221533 (p=0.02), which was found to be associated with psychotic manifestations in both disorders. Contrary to

that, Goes and collaborators (Goes, et al., 2009) genotyped 120 SNP and found that NRG1 is not a core risk factor to BD, but rather a risk factor to the development of psychotic symptoms within it (strongest P values for NRG241930-NRG243177-rs7819063).

This finding is especially important considering that it contributes to an explanation about the historical divergence in relation to the schizophrenia-BD relation: it may be the case that both phenotypes diverge considerably, and that an association holds as long as there are psychotic symptoms within the bipolar spectrum. We hypothesize that the conundrum between the classic authors in relation to the nosographic relations defined by both disorders actually relied on the variability among the cohorts that each one had in mind.

Neuregulin 1, schizophrenia and glutamate

The glutamatergic etiological hypothesis has become one of the most prominent in schizophrenia research. According to its most famous version, the syndrome is related with abnormal glutamatergic transmission and increased levels of free glutamate, which affect synaptic and dendrite structure, reduce signaling propagation through action potentials (as it impairs retransmission along WM Ranvier nodes) and in certain circumstances induce severe apoptosis (for a review: Bubeníková-Valesová, et al, 2008; Coyle, 2006).

The so called 'neuregulin1-glutamate hypothesis' has several slightly different versions. Considering the aforementioned NRG1 three layers model, it is possible to consider that the main point in all of them is that the third layer of the abnormal neuregulin 1 molecular cascade (final pathway) is a glutamate/NDMA (N-methyl-D-aspartate) imbalance which turns out to be highly neurotoxic. In relation to that, the canonical finding relates to the general importance of the neuregulin 1-ErbB pathway in glutamatergic neurotransmission (Fischbach, 2007), which in this case is associated with the perspective that neuregulin 1 hypofunction impairs NMDA activity, through a second messenger cascade, (Hahn, et al., 2006).

Mice constructs inactive for ErbB2/B4-mediated NRG1 were shown to develop normal general neurologic structure (frontal cortex, temporal cortex, hippocampus, etc.) but impaired dendrite maturation. As the study also revealed, this trait specifically introduces a post-synaptic (receptor) perturbation within the glutamatergic pathway (Barros, et al., 2009); which is reverted by clozapine intake ([1,4] diazepine). This perspective suggest that neuregulin1 is a track to the understanding of the fact that affected subjects are not born schizophrenic, but rather manifest the syndrome after during life, in the same context wherein neurological abnormalities become evident.

Neuregulin 1, schizophrenia and dopamine

Although we started the discussion on neurotransmitters talking about glutamate (due to the fact that it has indeed become central to schizophrenia's modeling), it is important to acknowledge that the classic hypothesis in schizophrenia's etiological studies is the so called 'dopaminergic hypothesis', which states that schizophrenia is caused by a dopaminergic imbalance, related with an excess of free dopamine in the frontal and temporal areas, and a decrease within the limbic circuits. This hypothesis is based on the fact that the mechanism of action of the most traditional antipsychotic drugs relates with the blockage of cortical dopaminergic signaling (for a review, a textbook: Kandel, et al, 2000).

With the uprising of the glutamatergic hypothesis this other one lost some of its attractiveness (one would say: in a sense it was comprised by the other); nevertheless, new dimensions of the dopaminergic hypothesis came to light in accordance with the recent tendency to associate schizophrenia's deficit with white matter abnormalities (connectivity impairs).

In that sense, a very interesting finding is that neuregulin1 abnormalities affect glial structure (underscoring oligodendrocyte density) which then affects white matter integrity (reducing myelin thickness), in association with an increase of cortical dopamine (Roy, et al., 2007). That is, it might turn out to be the case that the excess of dopamine is proved to be a byproduct of other events, but that these events rely on an abnormal neuregulin 1 function. This is in line with recent findings regarding the presence of ErbB4 activity on the substantia nigra of humans human (post mortem) and monkeys (in situ hybridization) (Zheng, et al., 2009).

Final remarks

This paper applies several bioinformatics techniques in order to review the role of neuregulin1 in schizophrenia research. In that sense, it was found that the polypeptide is involved in many molecular cascades that are underpinned by schizophrenia-related brain abnormalities. Moreover, it was shown that neuregulin1 is also associated with several other neurophysiological processes that are indirectly related with schizophrenia.

In our view, this last perspective is even more important than the former: currently, it is becoming clear that despite the specificity of schizophrenia's nosographic profile (that is, its singularity as a medical disorder), its neurobiological profile shares many features with affective (e.g. BD) and degenerative (e.g. AD) disorders, which seem to involve the role of neuregulin1 and other 'non-conventional' signaling molecules.

References

1. Abdolmaleky, H. M., Faraone, S. V., Glatt, S. J., & Tsuang, M. T. (2004). Meta-analysis of association between the T102C polymorphism of the 5HT2a receptor gene and schizophrenia. Schizophr Res, 67(1), 53-62.
2. Babovic, D., O'Tuathaigh, C. M., O'Connor, A. M., O'Sullivan, G. J., Tighe, O., Croke, D. T., et al. (2008). Phenotypic characterization of cognition and social behavior in mice with heterozygous versus homozygous deletion of catechol-O-methyltransferase. Neuroscience, 155(4), 1021-1029.
3. Barros, C. S., Calabrese, B., Chamero, P., Roberts, A. J., Korzus, E., Lloyd, K., et al. (2009). Impaired maturation of dendritic spines without disorganization of cortical cell layers in mice lacking NRG1/ErbB signaling in the central nervous system. Proc Natl Acad Sci U S A, 106(11), 4507-4512.
4. Benes, F. M., & Berretta, S. (2001). GABAergic interneurons: Implications for understanding

schizophrenia and bipolar disorder. [Editorial Material]. Neuropsychopharmacology, 25(1), 1-27.
5. Bubeníková-Valesová, V., Horácek, J., Vrajová, M., & Höschl, C. (2008). Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. Neuroscience & Biobehavioral Reviews, 32(5), 1014-1023.
6. Burden, S., & Yarden, Y. (1997). Neuregulins and Their Receptors: A Versatile Signaling Module in Organogenesis and Oncogenesis. Neuron, 18(6), 847-855.
7. Cabedo, H., Luna, C., Fernandez, A. M., Gallar, J., & Ferrer-Montiel, A. (2002). Molecular determinants of the sensory and motor neuron-derived factor insertion into plasma membrane. J Biol Chem, 277(22), 19905-19912.
8. Carrion-Baralt, J., Smith, C., Rossy-Fullana, E., Lewis-Fernandez, R., Davis, K., & Silverman, J. (2006). Seasonality effects on schizophrenic births in multiplex families in a tropical island. Psychiatric Research, 142(1), 93-97.
9. Carter, C. J. (2008). Schizophrenia Susceptibility Genes Directly Implicated in the Life Cycles of Pathogens: Cytomegalovirus, Influenza, Herpes simplex, Rubella, and Toxoplasma gondii. Schizophr Bull.
10. Chaudhury, A. R., Gerecke, K. M., Wyss, J. M., Morgan, D. G., Gordon, M. N., & Carroll, S. L. (2003). Neuregulin-1 and erbB4 immunoreactivity is associated with neuritic plaques in Alzheimer disease brain and in a transgenic model of Alzheimer disease. J Neuropathol Exp Neurol, 62(1), 42-54.
11. Chen, Y. J., Johnson, M. A., Lieberman, M. D., Goodchild, R. E., Schobel, S., Lewandowski, N., et al. (2008). Type III neuregulin-1 is required for normal sensorimotor gating, memory-related behaviors, and corticostriatal circuit components. J NEUROSCI, 28(27), 6872-6883.
12. Chen, Y. J., Zhang, M., Wang, P., Zhu, X. H., & Gao, T. M. (2008). [Neuregulin-1 temperature-dependently inhibits the long-term potentiation in the CA1 region in mouse hippocampal slices]. Nan Fang Yi Ke Da Xue Xue Bao, 28(10), 1771-1774.
13. Cheng, J. Y., Ko, J. S., Chen, R. Y., & Ng, E. M. (2008). Meta-regression analysis using latitude as moderator of paternal age related schizophrenia risk: high ambient temperature induced de novo mutations or is it related to the cold? SCHIZOPHR RES, 99(1-3), 71-76.
14. Coyle, J. (2006). Glutamate and Schizophrenia: Beyond the Dopamine Hypothesis. Cellular and Molecular Neurobiology, 26(4), 363-382.
15. Dean, B., Karl, T., Pavey, G., Boer, S., Duffy, L., & Scarr, E. (2008). Increased levels of serotonin 2A receptors and serotonin transporter in the CNS of neuregulin 1 hypomorphic/mutant mice. Schizophr Res, 99(1-3), 341-349.
16. Dejaegere, T., Serneels, L., Schafer, M. K., Van Biervliet, J., Horre, K., Depboylu, C., et al. (2008). Deficiency of Aph1B/C-gamma-secretase disturbs Nrg1 cleavage and sensorimotor gating that can be reversed with antipsychotic treatment. Proc Natl Acad Sci U S A, 105(28), 9775-9780.
17. Dias, Á. M., Queiroz, A. T. L., & Maracaja-Coutinho, V. Schizophrenia, brain disease and meta-analyses: Integrating the pieces and testing Fusar-Poli's hypothesis. [doi: DOI: 10.1016/j.mehy.2009.07.018]. Medical Hypotheses, In Press, Corrected Proof.
18. Falls, D. L. (2003). Neuregulins: functions, forms, and signaling strategies. Exp Cell Res, 284(1), 14-30.
19. Fan, J. B., Zhang, C. S., Gu, N. F., Li, X. W., Sun, W. W., Wang, H. Y., et al. (2005). Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. Biol Psychiatry, 57(2), 139-144.
20. Fischbach, G. D. (2007). NRG1 and synaptic function in the CNS. Neuron, 54(4), 495-497.
21. Ford, B. D., Liu, Y., Mann, M. A., Krauss, R., Phillips, K., Gan, L., et al. (2003). Neuregulin-1 suppresses muscarinic receptor expression and acetylcholine-activated muscarinic K+ channels in cardiac myocytes. Biochem Biophys Res Commun, 308(1), 23-28.
22. Gallinat, J., & Gudlowski, Y. (2008). The glutamate hypothesis of schizophrenia. Die Glutamathypothese der schizophrenie, 27(4), 317-325.
23. Georgieva, L., Dimitrova, A., Ivanov, D., Nikolov, I., Williams, N. M., Grozeva, D., et al. (2008). Support for neuregulin 1 as a susceptibility gene for bipolar disorder and schizophrenia. Biol Psychiatry, 64(5), 419-427.
24. Goes, F. S., Willour, V. L., Zandi, P. P., Belmonte, P. L., Mackinnon, D. F., Mondimore, F. M., et al. (2009). Family-based association study of Neuregulin 1 with psychotic bipolar disorder. Am J Med Genet B Neuropsychiatr Genet.
25. Gong, Y. G., Wu, C. N., Xing, Q. H., Zhao, X. Z., Zhu, J., & He, L. (2009). A two-method meta-analysis of Neuregulin 1(NRG1) association and heterogeneity in schizophrenia. Schizophrenia Research, In Press, Corrected Proof.
26. Hahn, C. G., Wang, H. Y., Cho, D. S., Talbot, K., Gur, R. E., Berrettini, W. H., et al. (2006). Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. Nat Med, 12(7), 824-828.
27. Hall, J., Whalley, H. C., Job, D. E., Baig, B. J., McIntosh, A. M., Evans, K. L., et al. (2006). A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. Nat Neurosci, 9(12), 1477-1478.
28. Hanninen, K., Katila, H., Saarela, M., Rontu, R., Mattila, K. M., Fan, M., et al. (2008). Interleukin-1 beta gene polymorphism and its interactions with neuregulin-1 gene polymorphism are associated with schizophrenia. Eur Arch Psychiatry Clin Neurosci, 258(1), 10-15.
29. Harrison, P. J., & Law, A. J. (2006). Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. Biol Psychiatry, 60(2), 132-140.
30. Irina J. Fox, H. I. K. (2005). Developmental profile of ErbB receptors in murine central nervous system: Implications for functional interactions. Journal of Neuroscience Research, 79(5), 584-597.
31. Jablensky, A., & Sartorius, N. (1988). Is schizophrenia universal? Acta Psychiatr Scand Suppl, 344, 65-70.
32. Kandel, E., Schwartz, J. H., & Jessell, T. M. (2000). Principles of Neuroscience. New York: McGraw-Hill.
33. Kendler, K., & Robinette, C. (1983). Schizophrenia in the National Academy of Sciences-National Research Council Twin Registry: a 16-year update. Am J Psychiatry, 140(12), 1551-1563.
34. Krivosheya, D., Tapia, L., Levinson, J. N., Huang, K., Kang, Y., Hines, R., et al. (2008). ErbB4-Neuregulin Signaling Modulates Synapse Development and Dendritic

Arborization through Distinct Mechanisms. J. Biol. Chem., 283(47), 32944-32956.
35. Kwon, O. B., Paredes, D., Gonzalez, C. M., Neddens, J., Hernandez, L., Vullhorst, D., et al. (2008). Neuregulin-1 regulates LTP at CA1 hippocampal synapses through activation of dopamine D4 receptors. Proc Natl Acad Sci U S A, 105(40), 15587-15592.
36. O'Tuathaigh, C. M., O'Connor, A. M., O'Sullivan, G. J., Lai, D., Harvey, R., Croke, D. T., et al. (2008). Disruption to social dyadic interactions but not emotional/anxiety-related behaviour in mice with heterozygous 'knockout' of the schizophrenia risk gene neuregulin-1. Prog Neuropsychopharmacol Biol Psychiatry, 32(2), 462-466.
37. Raedler, T. J., Bymaster, F. P., Tandon, R., Copolov, D., & Dean, B. (2006). Towards a muscarinic hypothesis of schizophrenia. Mol Psychiatry, 12(3), 232-246.
38. Robinson, D. R., Wu, Y.-M., & Lin, S.-F. (2000). The protein tyrosine kinase family of the human genome. Oncogenese, 19(49), 5548-5557.
39. Roy, K., Murtie, J. C., El-Khodor, B. F., Edgar, N., Sardi, S. P., Hooks, B. M., et al. (2007). Loss of erbB signaling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders. Proc Natl Acad Sci U S A, 104(19), 8131-8136.
40. Shim, S. S., Hammonds, M. D., & Kee, B. S. (2008). Potentiation of the NMDA receptor in the treatment of schizophrenia: focused on the glycine site. Eur Arch Psychiatry Clin Neurosci, 258(1), 16-27.
41. Stefansson, H., Sarginson, J., Kong, A., Yates, P., Steinthorsdottir, V., Gudfinnsson, E., et al. (2003). Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. Am J Hum Genet, 72(1), 83-87.
42. Steinthorsdottir, V., Stefansson, H., Ghosh, S., Birgisdottir, B., Bjornsdottir, S., Fasquel, A. C., et al. (2004). Multiple novel transcription initiation sites for NRG1. Gene, 342(1), 97-105.
43. Szabolcs Kéri, I. K., Imola Seres, Oguz Kelemen,. (2009). A polymorphism of the neuregulin 1 gene (SNP8NRG243177/rs6994992) affects reactivity to expressed emotion in schizophrenia. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150B(3), 418-420.
44. T. Karl, L. D., A. Scimone, R. P. Harvey, P. R. Schofield,. (2007). Altered motor activity, exploration and anxiety in heterozygous neuregulin 1 mutant mice: implications for understanding schizophrenia. Genes, Brain and Behavior, 6(7), 677-687.
45. Wehr, M. C., Reinecke, L., Botvinnik, A., & Rossner, M. J. (2008). Analysis of transient phosphorylation-dependent protein-protein interactions in living mammalian cells using split-TEV. BMC Biotechnol, 8, 55.
46. Williams, N. M., Preece, A., Spurlock, G., Norton, N., Williams, H. J., Zammit, S., et al. (2003). Support for genetic variation in neuregulin 1 and susceptibility to schizophrenia. Mol Psychiatry, 8(5), 485-487.
47. Wynn, J. K., Dawson, M. E., Schell, A. M., McGee, M., Salveson, D., & Green, M. F. (2004). Prepulse facilitation and prepulse inhibition in schizophrenia patients and their unaffected siblings. Biological Psychiatry, 55(5), 518-523.
48. Yarden, Y., & Sliwkowski, M. X. (2001). Untangling the ErbB signalling network. Nat Rev Mol Cell Biol, 2(2), 127-137.
49. Zhang, L., Fletcher-Turner, A., Marchionni, M. A., Apparsundaram, S., Lundgren, K. H., Yurek, D. M., et al. (2004). Neurotrophic and neuroprotective effects of the neuregulin glial growth factor-2 on dopaminergic neurons in rat primary midbrain cultures. J Neurochem, 91(6), 1358-1368.
50. Zheng, Y., Watakabe, A., Takada, M., Kakita, A., Namba, H., Takahashi, H., et al. (2009). Expression of ErbB4 in substantia nigra dopamine neurons of monkeys and humans. Prog Neuropsychopharmacol Biol Psychiatry.